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## Self-Organized Cerebral Organoids with Human-Specific Features Predict Effective Drugs to Combat Zika Virus Infection.

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**Authors:** Momoko Watanabe, Jessie E Buth, Neda Vishlaghi, Luis de la Torre-Ubieta, Jiannis Taxis, Baljit S Khakh, Giovanni Coppola, Caroline A Pearson, Ken Yamauchi, Danyang Gong, Xinghong Dai, Robert Damoiseaux, Roghiyeh Aliyari, Simone Liebscher, Katja Schenke-Layland, Christine Caneda, Eric J Huang, Ye Zhang, Genhong Cheng, Daniel H Geschwind, Peyman Golshani, Ren Sun, Bennett G Novitch

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### Public Summary:

The human brain possesses distinct structural and functional features that are not found in the lower species such as mice that are most often used to model disorders that impact human brain development and function. Accordingly, considerable attention has been placed on the development of methods to direct pluripotent stem cells to form human brain-like structures termed organoids or "mini-brains". While this emerging technology offers a great deal of promise for modeling a range of neurodevelopmental and neuropsychiatric disorders and may be further useful for therapeutic discovery, many challenges remain. Organoid techniques, for example, are often difficult to implement with many variabilities related to the starting cells used, and range of size and structural features between batches and individual organoids. Moreover, long-term tissue growth and survival has been limited, and it has been unclear how closely the neural tissue formed in organoids matches that seen in the human brain. In our study we describe optimized organoid culture methods that efficiently and reliably produce cortical and subcortical brain structures, and demonstrate that they are strikingly similar to those in the human fetal brain judged by multiple criteria. We also show that neurons within the organoids are functional and exhibit network-like activities, opening the door for future studies seeking to model neurological diseases. We lastly demonstrate the utility of the organoid system for investigating how Zika virus, an emerging worldwide public health threat, can infect and destroy neural progenitors in the developing brain, and identify several drugs that can block these damaging effects.

### Scientific Abstract:

The human cerebral cortex possesses distinct structural and functional features that are not found in the lower species traditionally used to model brain development and disease. Accordingly, considerable attention has been placed on the development of methods to direct pluripotent stem cells to form human brain-like structures termed organoids. However, many organoid differentiation protocols are inefficient and display marked variability in their ability to recapitulate the three-dimensional architecture and course of neurogenesis in the developing human brain. Here, we describe optimized organoid culture methods that efficiently and reliably produce cortical and basal ganglia structures similar to those in the human fetal brain in vivo. Neurons within the organoids are functional and exhibit network-like activities. We further demonstrate the utility of this organoid system for modeling the teratogenic effects of Zika virus on the developing brain and identifying more susceptibility receptors and therapeutic compounds that can mitigate its destructive actions.

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